EXHIBIT B

DEFENDANT ETHICON'S EXPERT REPORT ON MERSILENE MESH

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I. Qualifications

I am an expert consultant on matters concerning medical device regulations, policies, and procedures administered by the Food and Drug Administration (FDA) and related industry standards and best practices. I operate a registered business in the State of Virginia and the County of Fairfax, Virginia under the name Ulatowski Consulting, LLC.

I was awarded a Bachelor of Science degree in 1974 with a major in Microbiology from the Pennsylvania State University. In 1987 I was awarded a Master of Science degree in Physiology/Emphasis in Biomedical Engineering from Georgetown University, School of Medicine, in a collaborative program with Catholic University, Department of Engineering. I have additional college credits in computer science from the University of Maryland and Charles County Community College.

I was an employee of the Food and Drug Administration (FDA) from November 1974 until January 2011. During my 36 plus years of employment with FDA I held increasingly responsible positions, first for 7 years in what is now known as the Center for Drug Evaluation and Research (CDER), and the remaining years in the Center for Devices and Radiological Health (CDRH). CDRH is responsible for evaluating submissions for new medical devices, evaluating medical device clinical investigations, ensuring compliance with medical device laws and regulations administered by the FDA, conducting postmarket vigilance of marketed devices, and conducting research on medical devices.

From 1974 until 1978 I held the position of Microbiologist in the National Center for Antibiotic Analysis in CDER where I conducted laboratory analyses on antibiotics for regulatory certification purposes. From 1978 until 1980 I held the position of Consumer Safety Officer (CSO) in the Office of New Drug Evaluation (ONDE) in CDER. While at ONDE I was a product manager for the Anti-inflammatory Drugs Group and I also contributed to the Oncology and Radiopharmaceutical Drugs Groups. I was the Executive Secretary for the Arthritis Advisory Committee and managed the flow of work and outputs concerning investigational new drug applications (INDs) and New Drug Applications (NDAs). I also was the division lead on major issues such as the Drug Efficacy Study Implementation (DESI) program and the Radiopharmaceutical Drug Research Committee program. In this capacity I became thoroughly familiar with drug regulations, policies, and procedures as well as the related industry standards and best practices.

In 1980 I joined the Office of New Device Evaluation (NDE), Program Management Group, in the Bureau of Medical Devices (BMD) as a CSO. BMD was soon reorganized and joined with the Bureau of Radiological Health to form CDRH. NDE was renamed the Office of Device Evaluation (ODE).

In my first position in CDRH I was assigned to the Investigational Device Staff and was responsible for formulating policies and procedures to implement the new Investigational Device Exemptions regulation, 21 CFR Part 812, and other new human subject protection regulations dealing with informed consent and institutional review boards, 21 CFR Parts 50 and 56. I evaluated Investigational Device Exemption applications (IDEs) including protocols for clinical studies.

I also evaluated and quality controlled the IDE review work of all the divisions in ODE.

In 1988 I was promoted to the Director, IDE Staff. In that capacity I was responsible for managing and directing the IDE staff, for making final decisions on the sufficiency of IDE applications and the review of those submissions by FDA staff, and for IDE regulatory compliance in collaboration with the Office of Compliance, CDRH. In this position I was the CDRH expert on the IDE regulation, policies and procedures. I also became familiar with the industry standards and best practices related to the conduct of clinical studies on medical devices.

Later in 1988 I transferred to the position of Branch Chief, General Hospital Devices in ODE. As Branch Chief I managed and directed the branch staff, and was a primary reviewer of numerous IDE applications, Premarket Notification Submissions (510(k)s), Premarket Approval Applications, new product labeling, medical device reports (MDRs) and other types of regulatory submissions under the purview of my branch. The General Hospital Devices branch evaluated products classified by FDA under 21 CFR Part 880, General Hospital Devices. The products in this classification regulation include, for example, infusion pumps and ports, administration sets and intravascular catheters. When I assumed this position until the end of my FDA career the government classified me as a Supervisory Biomedical Engineer. In this position I was a subject matter expert in premarket submission and medical device reporting regulations, policies and procedures and knowledgeable about industry standards and best practices related to bringing a new device to the market.

In 1991 I was promoted to the position of Associate Director for General Devices in ODE. The scope of my responsibilities expanded to include the premarket evaluation of surgical devices classified under 21 CFR Part 878 as well as the previously assigned general hospital products. In this capacity I had broader influence on guidance, policy and procedure development spanning the entire ODE. I formulated guidance, policies, and was directly involved in the review of many significant new products such as medical lasers and computerized medical systems. As an Associate Division Director, and earlier as a Branch Chief, I instructed ODE reviewers on the policies and procedures regarding premarket submissions. My training to staff included, for example, how to identify and assess predicates and reference device information contained in a 510(k), how to assess technological characteristics and performance data.

In 1996 I was promoted to the Director, Division of Dental, Infection Control and General Hospital Devices in ODE. In this position I assumed responsibility for more product areas and all the premarket regulatory activities associated with those product areas. For example, during the course of my tenure as an ODE division director, I assumed responsibility for anesthesiology devices. During my tenure with FDA I reviewed and made agency decisions on thousands of 510(k)s and dozens of PMAs.

During my tenure at FDA I also participated as a member on FDA committees, national and international standards committees, and the Global Harmonization Task Force (GHTF).[1] The GHTF created guidance

[1] The Global Harmonization Task Force has transitioned to the International Medical Device Regulators Forum, www.imdrf.org.

concerning industry standards and best practices related to the life cycle of medical devices and in vitro diagnostics. I was Co-Chair of the FDA committee that created the existing standards program in CDRH. The CDRH standards program evaluates national and international standards to determine if FDA should recognize and utilize them as means to support product development and premarket submissions. During my tenure I also wrote the first FDA guidance documents on infusion pumps and accessories, infusion ports, sterilizers, chemical germicides, and guidance on labeling of devices intended for reuse. I was a member of several Association for the Advancement of Medical Instrumentation (AAMI) and International Standards Organization (ISO) sterilization standards committees.

In 2003 I was promoted to Director, Office of Compliance, CDRH. As the Office of Compliance Director I supervised a large staff that was responsible for ensuring industry and human subject research compliance with the medical device, radiological health, and human subject protection laws and regulations administered by FDA. I had many duties including, for example, directing inspections of medical device manufacturing facilities and clinical research facilities, evaluating Quality System and MDR-related inspection reports and taking regulatory action based on those reports, classifying recall actions, creating risk management strategies, evaluating advertising, labeling and promotional literature, leading the FDA Device Field Committee,[2] and directing responses to violations of import/export and registration laws and rules. In this position I was a subject matter expert in FDA law and regulations concerning medical devices and knowledgeable about related industry standards and best practices.

I transitioned to the position of Senior Advisor for Enforcement in October 2010 in anticipation of my retirement and to allow an orderly succession of leadership. During the last four months of my FDA career I led a team formulating strategies in advance of Congressional user fee reauthorization deliberations and I provided expert advice to senior FDA leadership on premarket and compliance programs. The Commissioner awarded me for my work on user fee legislation.

During my employment with FDA I received virtually every type of award FDA can bestow including the Distinguished Career Service Award, Award of Merit, Commendable Service Awards, and numerous other individual and group awards. I maintained my management and regulatory expertise during the course of my career by attending numerous professional meetings, courses and seminars. I was frequently an invited speaker or major participant at regulatory and professional conferences here and abroad such as those held by the Food and Drug Law Institute, Regulatory Affairs Professional Society, Pharmaceutical Research and Manufacturers of America, and the American Society for Quality. In 2008 Medical Device and Diagnostic Industry News named me to their "100 Notable People" in the medical device industry. I continue to remain current on FDA device regulations, policies and procedures and on related industry standards and best practices.

I am currently an independent consultant. I provide consulting services to clients on premarket submissions, postmarket surveillance, labeling, promotion and advertising, and quality systems. I advise medical device and drug manufacturers on compliance matters. I provide litigation

[2] The Device Field Committee members include chief inspectors, senior compliance managers, and other senior FDA officers.

testimony on FDA regulations, policies and procedures and industry standards and best practices. I continue to be an invited speaker at professional and industry meetings. Under the auspices of the Department of Commerce and the USAID, I trained international regulators on global medical device premarket and postmarket regulatory policies and procedures and on related industry standards and best practices in October and November 2013 and again in March and May of 2014.

A copy of my curriculum vitae is attached as Appendix A.

NDA Partners LLC bills for my time in this litigation at a rate of $600/hr.

The list of materials that I considered in forming my opinions is attached as Appendix B. I did not rely on any commercial confidential or trade secret information obtained during the course of my employment with FDA in forming my opinions.

II. FDA's Mission, Device Statutory and Regulatory Provisions, and Industry Standards and Best Practices Relevant to the Subject Litigation

II.A. Overview

FDA is a consumer protection agency that has roots stretching back to the turn of the last century. Its statutory authority is derived from the Federal Food, Drug, and Cosmetic Act (the act) (21 USC 301 et seq.)[3] and other acts that have been amended from time to time. Regulations implementing the statutory provisions are published in Title 21, Code of Federal Regulations (21 CFR). The first medical device amendments to the act were enacted on May 28, 1976 and there have been additional amendments in the intervening years.[4]

FDA regulates medical devices. MERSILENE MESH is a medical device. A medical device is defined under 21 USC §321(h) as:

> *"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is (1) recognized in the National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals, or (3) intended to affect the structure or function of the body in man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 360j(o) of this title."*

[3] References to the act are stated according to United States Code.
[4] Amendments to the act, http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/default.htm.

FDA regulates the entire life cycle of medical devices. For example, FDA evaluates investigational studies for new products before the studies commence,[5] it inspects manufacturing facilities,[6] it evaluates marketing applications, and it monitors the safety and effectiveness of devices during the entire course of their use. FDA regulations govern each of these activities and FDA makes available related guidance documents to inform industry, FDA staff and the public of means to address regulatory requirements.

Industry standards and best practices supplement FDA law and regulations to assist manufacturers throughout the life cycle of a medical device. These standards and best practices are applied by manufacturers in bringing devices to the market, in manufacturing devices, and in postmarket monitoring devices in the marketplace.

II.B. FDA's Medical Device Program

CDRH is the primary organization within FDA that regulates medical devices. Other FDA Centers also have authority to regulate medical devices, primarily those that are a constituent of a combination product. Combination products are therapeutic or diagnostic products that consist of more than one regulated article, e.g., drug/device, and biological/device. Each combination product is regulated by the Center given primary jurisdiction for the specific combination product.

CDRH has over 1000 employees and is organized into offices. For example, ODE is responsible for review of new devices, except for in-vitro diagnostics and radiologic products, the Office of Compliance (OC) is responsible for compliance and enforcement activities and the Office of Surveillance and Biometrics (OSB) is primarily responsible for evaluating medical device reports (MDRs), conducting epidemiology activities, and statistical reviews.

Information from each office within CDRH is integrated by computer systems available for all FDA employees to access and use in the course of performing their jobs. For example, a compliance officer in OC can easily access MDRs, inspection records, and premarket records for specific companies and devices.

CDRH leverages resources from within and outside FDA to accomplish its mission. CDRH leverages the resources of the Office of the Associate Commissioner for Regulatory Affairs, the organizational home of FDA's inspectors, to conduct device manufacturer and clinical investigator inspections. CDRH uses non-FDA, so-called "special government employees", in the fields of medicine, engineering and statistics, and third parties to assist in premarket and compliance activities.

CDRH obtains information on medical devices for review and analysis by many means. For example, it receives required submissions according to regulations, it proactively collects information and evidence during

[5] FDA does not approve "non-significant risk" devices before studies commence. This evaluation and approval is delegated to institutional review boards (21 CFR Part 56).

[6] FDA has authority to inspect all facilities subject to inspection, e.g., all places related to quality system and medical device reporting activities (21 U.S.C. §374).

inspections, it uses public sources of information, and increasingly it relies on regulatory bodies in other countries to provide information on imported FDA-regulated products. FDA has extensive test facilities and conducts laboratory and engineering analyses on regulated products for compliance, premarket, and postmarket surveillance purposes.

II.C. Prohibited Acts, Misbranding and Adulteration and FDA Enforcement of Laws and Regulations It Administers

II.C.1. Prohibited Acts

The Federal Food, Drug, and Cosmetic Act is a law enforcement statute. The law prohibits specific acts or the causing thereof, such as:[7]

> The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded;
>
> The adulteration or misbranding of any food, drug, device, or cosmetic in interstate commerce; and
>
> The receipt in interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.

II.C.2. Adulteration

The act states that a device shall be deemed to be adulterated, in part (paraphrased):[8]

> If the methods used in, or the facilities or controls used for, its manufacture, packing, storage, or installation are not in conformity with applicable good manufacturing practices.
>
> It is a Class III device and is not the subject of a premarket approval application.

II.C.3. Misbranding

The act states that a device shall be deemed to be misbranded, in part (paraphrased):[9]

> If its labeling is false or misleading in any particular.

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[7] FDA applies regulatory procedures in determining whether a violation exists based upon the evidence it gathers, and when deciding the penalties or actions it may apply to remedy the violation. Penalties and violations are subject to the final concurrence by the court with jurisdiction. The violator is provided due process, e.g., to contest or appeal a charge of a FDCA violation.

[8] 21 U.S.C. §351(h).

[9] 21 U.S.C. §352.

> Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users, except that where any requirement of clause (1) of this paragraph, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement;
>
> It is dangerous to health when used in the dosage or manner or with the frequency or duration prescribed, recommended, or suggested in labeling thereof;
>
> If a notice or other information respecting it was not provided as required by section 510(k); or
>
> For which there has been a failure or refusal to give required notification or to furnish required material or information such as section 519, medical device reports.

The act also states the following regarding misbranding:[10]

> If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.

The misbranding provisions of 21 USC §§352(q) and (r) relating to advertising for restricted devices did NOT apply to MERSILENE MESH because it is not a restricted device.[11]

II.C.4. Tools Available to FDA to Enforce the Laws and Regulations It Administers

The FDA Regulatory Procedures Manual (RPM)[12] directs FDA personnel on internal procedures to be used in processing domestic and important regulatory and enforcement matters. While the RPM is intended mainly to

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[10] 21 USC §321(n).

[11] Devices must be designated by FDA as "restricted," either by a regulation promulgated under 21 USC §360j(e), or by a premarket approval application (PMA) approval order pursuant to 21 USC §360e(d)(1)(B)(ii)). Neither applies to MERSILENE MESH.

[12] FDA Regulatory Procedures Manual, http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176446.htm.

provide guidance to FDA inspectors, investigators, and compliance officers, the document is useful to all of FDA and informative to the device industry.

The RPM describes the tools and actions FDA may take to help ensure compliance with the laws and regulations it administers.[13] Those actions include (1) advisory, administrative, judicial and import actions, and (2) recall, emergency and other procedures. The key offices responsible for working together on these medical device actions and procedures include the Office of Compliance/CDRH, the Office of the Associate Commissioner for Regulatory Affairs, and the Office of Chief Counsel. Other FDA offices contribute only as needed.

According to the RPM, "When it is consistent with the public protection responsibilities of FDA and depending on the nature of the violation, it is FDA's practice to give individuals and firms an opportunity to take voluntary and prompt corrective action before it initiates an enforcement action. **Warning and Untitled Letters**, both advisory actions, are issued to achieve voluntary compliance and to establish prior notice. The use of these letters and the prior notice policy are based on the expectation that most individuals and firms will voluntarily comply with the law."

The FDA compliance office may exercise enforcement discretion when deciding whether to take enforcement action. Also, the RPM notes "there are instances when issuing a Warning Letter is not appropriate, and, as previously stated, a Warning Letter is not a prerequisite to taking enforcement action. Examples of situations where the agency will take enforcement action without necessarily issuing a Warning Letter include:

1. The violation reflects a history of repeated or continual conduct of a similar or substantially similar nature during which time the individual and/or firm has been notified of a similar or substantially similar violation;
2. The violation is intentional or flagrant;
3. The violation presents a reasonable possibility of injury or death;
4. The violations, under Title 18 U.S.C. 1001, are intentional and willful acts that once having occurred cannot be retracted. Also, such a felony violation does not require prior notice. Therefore, Title 18 U.S.C. 1001 violations are not suitable for inclusion in Warning Letters; and,
5. When adequate notice has been given by other means and the violations have not been corrected, or are continuing."

Relevant administrative actions include Section 305 notices (Citations), Section 305 meetings, administrative detention of devices, and civil money penalties (CMPs). **Detention and civil money penalties** are the most common actions taken. FDA may detain devices for a period of up to 30 calendar days if, during an inspection, the FDA has reason

[13] The 1976 medical device amendments to the act added new authorities to FDA's regulation of medical devices. Prior to 1976 the act permitted inspection of device manufacturing facilities and certain enforcement actions noted in this section of the report. There were no premarket submission requirements for devices unless those devices were regulated as drugs, e.g. sutures and intraocular lenses are two such examples.

to believe the devices are adulterated or misbranded. The intent of administrative detention is to protect the public by preventing distribution or use of violative devices until FDA has had time to consider the appropriate action to take and, where appropriate, to initiate a regulatory action. The action of choice, in most cases, is a seizure. CMPs are monetary penalties that are assessed by FDA for violations of the law and regulations.

Some relevant judicial actions include seizure, injunction and prosecution. For a **seizure**, the United States of America, as Plaintiff, proceeds under the Supplemental Rules for Certain Admiralty and Maritime Claims (Supplemental Rules) by filing a Complaint for Forfeiture and obtaining a warrant for arrest of the device, directing the United States Marshal to seize (take possession or place in constructive custody of the court) the device. An **injunction** is a civil judicial process initiated to stop or prevent violation of the law, such as to halt the flow of violative products in interstate commerce, and to correct the conditions that caused the violation to occur. FDA can refer cases to the Department of Justice for **criminal prosecution.**

As part of import operations the government may **refuse to admit** devices for import and can **detain** devices upon import. Section 801(a) of the Federal Food, Drug, and Cosmetic Act directs the Secretary of the Treasury to issue a Notice of Refusal when it appears from examination of samples, or otherwise, that an imported shipment is in violation. This Section also orders the destruction of any such shipment refused admission, unless it is exported within 90 days of the date of the notice, or within such additional time as may be permitted pursuant to such regulations. FDA may refuse to admit devices based on information, *other than the results of examination of samples that causes an article to appear to violate the Act*.

Two common additional procedures are the **regulatory meeting** and "**It has come to our attention**" letters. A Regulatory Meeting is a meeting requested by FDA management, at its discretion, to inform responsible individuals or firms about how one or more products, practices, processes, or other activities are considered to be in violation of the law. FDA is not required to hold a Regulatory Meeting and, except for a few specifically defined areas, is not required to provide any other form of notice before taking an enforcement action. An "It has come to our attention letter" may be issued by OC where a potential violation has been observed and FDA requests information to assess the activity. It is not an advisory or enforcement letter.

Advisory, enforcement or other compliance actions are generally initiated by OC[14] or the Office of the Associate Commissioner for Regulatory Affairs based upon potential violations identified by many sources, e.g., inspections, public or industry complaints, FDA surveillance of public information, or internal agency referrals. Only compliance and enforcement staff with the delegated responsibility can initiate, process or issue an enforcement or advisory action.

The Office of Compliance assesses internal agency referrals of a

[14] The Office of In Vitro Diagnostic Devices and the Office of Surveillance and Biometrics can initiate compliance actions but the actions must be processed and approved through the Director of Compliance.

potential violation, e.g., a referral from ODE. The Office of Compliance's initial assessment includes, for example, a determination if the referral describes an activity that may be a violation, whether there is adequate documentation of the activity, and an analysis of the risk to the public health.

II.D. The Life Cycle of Medical Devices; Designing and Testing Medical Devices Prior to Marketing; Risk Management Throughout the Device Life Cycle

FDA, other global regulatory counterparts, and the device industry have characterized the development and marketing of a medical device as a life cycle. The cycle begins with the manufacturer developing a concept for a new or modified device, the cycle proceeds through design phases, the design is transferred to manufacturing, the product is manufactured and the device is placed on the market. The cycle is complete when the device becomes obsolete or if the device is modified.

The design controls provisions of the FDA Quality System regulation, 21 CFR §820.30, provide the general control requirements a device manufacturer must incorporate into its design and development procedures and processes. Design controls consist of requirements for (1) design and development planning, (2) design inputs, (3) design outputs, (4) design reviews (5) verifying that design outputs meet design inputs requirements (6) validating that the finished device meets defined user needs and intended uses, and (7) transferring the design to manufacturing. Documentation of design activities is captured in the Design History File. Design changes before implementation are a managed process with the need for review and approval of changes, verifications and revalidation of the design, when needed.

The Quality System regulation characterizes these and other quality requirements as basic requirements.[15] Industry standards and best practices serve to supplement the regulations, for example, by helping manufacturers determine the form and manner of recordkeeping indicated basically in regulation, and the procedures and specific policies the device manufacturer will follow when monitoring its devices while they are in the marketplace.

FDA recognizes that manufacturers are constantly developing new and improved devices and bringing these devices to the market even while prior versions of the same type of device continue to be legally marketed. The prior versions of devices remain on the market until the manufacturer decides to discontinue these previously marketed versions.

There is no requirement to tell FDA, e.g., in marketing application (aka. a Premarket Approval Application or 510(k) notification), about next generation devices in the development pipeline. However, manufacturers' design and quality data concerning devices being developed are subject to FDA inspection.

Risk management is a life cycle process. Risk management is the systematic application of management policies, procedures, and practices to the tasks of identifying, analyzing, controlling, and

[15] 21 CFR §820.1(a).

monitoring risk.[16] Risk management is intended to be a framework within which experience, insight, and judgment are applied to successfully manage risk. Risk analysis, part of risk management, is required by the Quality System regulation as part of design validation.[17] Risk management also is an important industry standard and best practice, and FDA has recognized the international Risk Management standard, ISO 14971.[18] FDA has also cited ISO 14971 in guidance concerning benefit/risk determinations.[19]

Risk management by a manufacturer begins with the initial development of the design input requirements and assessment of risks known or anticipated at the initial stages of product design. In this way, unacceptable risks can be identified, to the degree possible, and managed earlier in the design process when changes are easier to make and less costly. Preliminary Hazard Analyses, Failure Modes and Effects Analyses (FMEAs),[20] Hazard and Operability Studies, Hazard Analyses and Critical Control Point, Fault Tree Analyses are examples of commonly used tools in the risk analysis process. These analyses are often contained in Risk Management Reports containing the risk assessment, risk control, residual risk and risk acceptability elements of the risk management process for a specific type of device.

Risk management is an iterative process. As the international risk management standard notes, the manufacturer should monitor production and post-production information for data and information that may affect the device risk.

II.E. Device Classification and Regulatory Paths to the Market

II.E.1. Classification

Classification is fundamental to FDA's regulation of medical devices after 1976. The act establishes three classes of devices, Class I, II, and III.[21] The act provides mandatory regulatory controls for each class to provide reasonable assurance of safety and effectiveness for devices within each class. The act sets out the qualifications of members of medical panels charged with recommending to the FDA the proper classification of types of devices.[22]

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[16] See discussion of risk management in FDA Design Control Guidance, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070627.htm. The International Standards Organization (ISO) Standard 14971:2007 is commonly utilized to develop the processes and procedures associated with risk management activities.

[17] 21 CFR §820.30(g).

[18] ISO 14971 FDA recognition, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/detail.cfm?standard__identification_no=30268.

[19] Factors to Consider When Making Benefit/risk Determinations in Medical Device PMAs, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm267829.htm.

[20] Device Design Safety Analyses are similar to FMEAs.

[21] 21 USC §360c.

[22] 21 USC §360c (b)-(d).

The FDA classifies devices according to the risks they present. Class I devices are the lowest risk and are only is subject to "General Controls" including, for example, adulteration and misbranding, registration and listing, adverse event reporting, and good manufacturing practice (quality system) requirements.

Class II devices present a greater risk and, in addition to General Controls, Class II devices are generally subject to defined regulatory "Special Controls" that may include, for example, a specific guidance document, or an additional labeling requirement.

Class III devices generally present the greatest risk and are subject to Premarket Approval but also must meet General Controls. The Premarket Approval process only applies to Class III devices. If a device "presents a potential unreasonable risk of illness or injury," it must be in Class III.[23] For this reason, FDA placement of a device in Class II represents a determination that, with whatever special controls the FDA has imposed in addition to general controls, it does not present "a potential unreasonable risk of illness or injury." Class II devices are not eligible for Premarket Approval, i.e., one cannot submit a PMA for a Class II device.

FDA, based on the recommendations of panels of experts relevant to the devices under consideration, was tasked with classifying all devices on the market on May 28, 1976, when the device amendments came into effect, into one of the three classes based upon the panels' assessments of safety and effectiveness of those devices and controls necessary for these devices to provide reasonable assurance of their safety and effectiveness. One exception is about a dozen types of devices that were on the market and regulated by FDA as drugs prior to May 1976 were by law automatically Class III devices. The thousands of remaining devices on the market prior to 1976 were grouped into generic types and classified. The classifications for all the types of devices are detailed in 21 CFR, Parts 862-892.

Surgical mesh is one such type of device that FDA has classified based on FDA expert panel recommendations. In 1982 the FDA's General and Plastic Surgery Device Classification Panel, after public notice and comment, proposed that surgical mesh be classified Class II (47 FR 2810).[24] The panel cited, among other things, clinical literature on the use of surgical mesh in hernia repair. The panel found that surgical mesh "has an established history of safe and effective use." The panel considered such issues as "long-term adverse tissue reaction," infection, and implant rejection. After considering those risks, it determined that "premarket approval is not necessary to provide reasonable assurance of the safety and effectiveness of the device."[25]

The classification into Class II for surgical mesh became final in 1988 with the adoption of 21 CFR §878.3300 (53 FR 23872).[26] The FDA expressly refused to place surgical mesh in Class III. Citing clinical literature on, among other things, implantation of polymeric implants, the FDA

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[23] 21 USC §360c(a)(1)(C)(i)(II).

[24] The panel consisted of physicians and those with other scientific disciplines.

[25] 47 FR 2810.

[26] Surgical mesh intended for pelvic organ prolapse has been reclassified to Class III.

said it "believes that the biocompatibility of the materials now being used in these devices has been established through their successful use for a number of years…. Clinical experience with [surgical mesh] has established the persons for whose use the devices are intended and the proper conditions of use. FDA has determined that the probable benefit to health from proper use of these devices outweighs and [sic] likelihood of illness or injury resulting from their use." At the same time, it found special controls could be needed because at that time past use did not yet provide "adequate evidence on long-term biocompatibility."[27]

For specific devices not on the market on or before May 28, 1976, the act provides that any device intended for human use which was not introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976 is classified in class III unless the device is found by FDA to be "substantially equivalent" to a type of device (a predicate device) classified into class I or II.[28] FDA determines whether the new device is substantially equivalent to a predicate by its review of what the act describes as a "report" submitted to FDA preceding introduction of the device into interstate commerce. This "report" is the 510(k) notification.

II.E.2. Paths to the Market

As noted, the medical device amendments to the Federal Food, Drug and Cosmetic Act were enacted in 1976. Medical devices that were on the market before then are considered "grandfathered" devices and may remain on the market until, for example, the manufacturer decides to no longer commercialize the device, it is recalled by the manufacturer, the device is a Class III device for which FDA now requires a PMA and no PMA for the device is submitted and approved, FDA removes the device by an enforcement action, or the device is significantly modified and then becomes subject to a premarket submission.[29] MERSILENE MESH is a pre-1976 "grandfathered" device, which by virtue of the FDA's 1988 classification action, has been placed in Class II.[30]

There are two main regulatory paths to the market for new, post 1976 medical devices. One path is FDA approval of a premarket approval

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[27] See FDA guidance for surgical mesh that is not a special control, https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073791.pdf.

[28] New devices equivalent to some types of pre-amendments Class III devices were permitted to be placed on the market via a 510(k) until FDA required PMAs for that type of device.

[29] 21 U.S.C. §360c.

[30] There are no premarket submissions to FDA for MERSILENE MESH. Literature refers to pre-1976 MERSILENE MESH. See Zargar et. al., The regulatory ancestral network of surgical meshes, PLoS ONE 13(6):e0197883.https://doi.org/10.1371/journal.pone.0197883. PROLENE MESH and MERSILENE MESH both cited as pre-1976 meshes. See also Haskey, RS et.al., Difficult hernias: Mersilene mesh in the repair of hernias. J. Kan. Med. Soc., 1975;76:239. See also Chevrel, J.P., Polyester Mesh for Incisional Hernia Repair, Incisional Hernia, page 327-333. Springer, Berlin, Heidelberg. See also Gynemesh PS 510(k), K013718 that refers to preamendments MERSILENE MESH, ETH-00819.

application (PMA) for a Class III device[31] and the other is by FDA clearance of a premarket notification submission for a Class II device, commonly known as a 510(k) submission. Virtually all Class I devices and many Class II devices are exempt from the requirement to submit a 510(k) submission.

The logical path, i.e., PMA or 510(k), for a manufacturer to consider for a new device depends mainly on whether there is an existing regulatory classification for a similar generic type of device. For example, there is a regulatory classification of Class II for the generic group "surgical mesh" based on the FDA panel recommendations in 1982 and FDA's final decision in 1988.[32] Surgical mesh intended for use, i.e., labeled for that use, in hernia repair or for stress urinary incontinence, are types of Class II surgical mesh; therefore, the only path for a manufacturer to follow to obtain market clearance for a new hernia mesh device is to submit a 510(k) notification to FDA using a legally marketed predicate from the same classified surgical mesh group.

For the purposes of this report on MERSILENE MESH, I will elaborate on the 510(k) submission path to clearance for marketing since it was a surgical mesh of the type classified by FDA as a Class II device.

The act describes the form and manner of the "report", aka, 510(k) notification.[33] It provides, in part, that each person who is required to register and who proposes to begin the introduction or delivery for introduction into interstate commerce for commercial distribution of a device intended for human use shall, at least ninety days before making such introduction or delivery, "report" to FDA (in such form and manner as FDA shall by regulation prescribe) (1) the class in which the device is classified under Section 360c and (2) action taken by such person to comply with requirements under 21 USC §360d (standards) or Section 360e (premarket approval) which are applicable to the device. These original fundamental provisions of a 510(k) "report" have been expanded, defined, and enriched in several amendments to the act after 1976.

The term "substantially equivalent", which I have noted above, is at the core of classification by means of a 510(k) submission. An amendment to 360c(i) of the act incorporated a definition of this term that FDA had previously included in guidance. According to the act, "substantially equivalent" or "substantial equivalence" means that the new device has the same intended use as the predicate device and the same technological characteristics, or if it does not have the same characteristics then information submitted demonstrates that the new device is as safe and effective as the predicate and does not raise different questions of safety and effectiveness than the predicate device. The FDA review criteria discussed below for a 510(k) submission incorporate this statutory provision and expand upon it.

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[31] PMAs for pre-amendment Class III devices are not required until FDA publishes a final rule requiring PMAs. Until then an applicant for a new equivalent pre-amendment Class III device must obtain FDA market clearance via the 510(k) process.
[32] 21 CFR §880.3300.
[33] 21 U.S.C. §360(k).

According to a recent FDA guidance, safety and effectiveness is an inherent part of FDA's determination of substantial equivalence.[34] The guidance states, "The 510(k) review standard (substantial equivalence of a new device to a legally marketed (predicate) device) differs from the PMA review standard (reasonable assurance of safety and effectiveness). The 510(k) review standard is comparative, whereas the PMA standard relies on an independent demonstration of safety and effectiveness. Nonetheless, the principles of safety and effectiveness underlie the substantial equivalence determination in every 510(k) review."

This is especially true where the new device is "substantially equivalent" to a device in a group that has been classified into Class II based on the recommendations of an FDA medical advisory panel.

II.E.3. Premarket Notification Submissions

The 510(k) regulation, 21 CFR Part 807 Subpart E, describes when a 510(k) is required. In part, a 510(k) is required for a device being marketed for the first time or for a marketed device that is to be significantly changed or modified in design, components, method of manufacture, or intended use.[35]

The regulation under 21 CFR §807.87 also describes information required in a 510(k). The 510(k) must include, in part: labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for its use; comparisons to other legally marketed devices; and any other information the FDA needs to determine substantial equivalence.[36] FDA's review of 510(k) data and information is rigorous and thorough.

There is ample FDA guidance pertaining to 510(k)s. Some FDA guidance applies to the submission process in general[37] while product-specific guidance, if available, provides more details on format and content for a 510(k). The details may include standards that should be applied, specific tests and outputs, and specific labeling recommendations.

Guidance is not mandatory. FDA Good Guidance Practices (GGPs) state "You (for instance a manufacturer) may choose to use an approach other than the one set forth in a guidance document. However, your alternative approach must comply with the relevant statutes and

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[34] Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)], http://www.fda.gov/downloads/medicaldevices/.../ucm284443.pdf.

[35] Many Class I and lower risk Class II devices are exempt from 510(k) notification requirements.

[36] "[A]ny other information" may include, for example, preclinical or clinical data, or revised labeling.

[37] 510(k) Submission Process, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm070201.htm.

regulations."[38] GGPs also state "Although guidance documents do not legally bind FDA, they represent the agency's current thinking. Therefore, FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence."

FDA issued guidance for surgical mesh in 1999, which is applicable to mesh labeled for treatment of hernias or stress urinary incontinence.[39] The guidance recommends that 510(k)s for surgical mesh include, in part: a summary of safety and effectiveness or a statement that such information is available upon request, specification of all material components of the device, manufacturing information, packaging information, product characterization, and labeling. The document states a final consideration that additional information may be required as technological advances continue but it does not specifically identify the need for clinical data. The initiation of marketing of MERISLENE MESH predated the FDA guidance.

From its review of a 510(k) submission, the FDA may determine, by order, that a 510(k) submission is substantially equivalent (SE), SE with limitations,[40] not substantially equivalent (NSE), or that additional information is needed to render a decision (AI). FDA considers a device that it finds SE by means of a 510(k) to be "cleared." A device is "approved" only by an FDA approval order for a premarket approval application.

Prior to the Safe Medical Devices Act of 1990 (SMDA)[41] manufacturers could go to market after 90 days of submission of the 510(k) unless FDA intervened beforehand by either calling the submitter to "hold" the review clock, or by issuing an Additional Information (AI) or Not Substantially Equivalent (NSE) letter. Now, FDA must issue an order for a 510(k) declaring the device equivalent before the device may be marketed.

The current language in the standard FDA Additional Information (AI) letters that "You may not market this device until…you have received a letter from FDA allowing you to do so" was included in the form AI letter after SMDA in 1990. FDA may apply enforcement discretion regarding this provision in certain cases.[42] The AI letter is also an

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[38] 21 CFR §10.115.

[39] Guidance for Industry and/or for FDA Reviewers/Staff and/or Compliance - Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073790.htm.

[40] Determination of Intended Use for 510(k) Devices; Guidance for CDRH Staff (Update to 98-1), http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm082162.htm.

[41] SMDA, The Safe Medical Devices Act of 1990 (P.L. 101-629), which amended the FFD&C Act (21 U.S.C. 201 et seq.), was signed into law on November 28, 1990.

[42] Two cases where enforcement discretion has been applied include (1) a device is modified after a recall and continues to be marketed and then changes to the device are submitted in a 510(k). (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080297.htm), and (2) submission of a 510(k) after a device has been marketed when FDA requests voluntary submission and ODE makes

administrative letter issued by the Office of Device Evaluation simply to convey to the manufacturer the information ODE needs to complete its review. It is not an enforcement action.

FDA notes that there are "…many changes in the evolution of a device."[43] When making changes to a marketed device a manufacturer determines that a new 510(k) is needed according to regulation when:

> the device is one that the person currently has in commercial distribution or is reintroducing into commercial distribution, but that is about to be significantly changed or modified in design, components, method of manufacture, or intended use. The following constitute significant changes or modifications that require a premarket notification:
> (i) A change or modification in the device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process.
> (ii) A major change or modification in the intended use of the device.[44]

The FDA guidance document "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), January 10, 1997" was developed to help assist manufacturers in deciding when a change to a device was "significant" or "major."[45] This guidance was revised in 2017. FDA noted in the 1997 version of the guidance "To be certain that a decision on when to submit a 510(k) is correct, one would probably need to enumerate all device types and all potential types of changes and then match each combination of device and change with a decision. Given that there are thousands of individual device types and possibly tens or hundreds of enumerable changes, this would be an impossible task. Furthermore, the resultant guidance would fill volumes, would probably be difficult to use, and would be unlikely to keep pace with an ever-changing technology."

While the original and revised guidance provides general guidance on making decisions regarding changes to devices it is clear that FDA relies on manufacturer compliance with the Quality System regulation as one way of ensuring device safety and effectiveness. The guidance states, "For many types of changes to a device, it may be found that a 510(k) is not necessary, and the Agency may reasonably rely on good manufacturing practices (either as implemented under the 1978 GMP or the Quality Systems regulation) to continue to assure the safety and effectiveness of the changed device. This reliance is enhanced when manufacturers document their decision-making based on their testing results or other design validation criteria." Also, manufacturers "must have a process in place to demonstrate that the manufactured device meets the change in design specifications (or the original

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an enforcement referral to OC, e.g., a manufacturer makes a change to a device it deemed not significant but is later deemed significant by FDA.

[43] FDA Guidance: Deciding When to Submit a 510(k) for a Change to an Existing Device.

[44] 21 CFR §807.81(3).

[45] Original guidance retained in my personal records. Updated guidance, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm.

specifications, if no change was intended). They must keep records, and these records must be made available to an FDA inspector." The guidance states, "No matter how carefully this guidance is applied, there will still be decisions in a "gray area" that manufacturers will have to make."[46] Manufacturers are encouraged, but not required, to contact FDA when the proposed change is not addressed in the guidance flowcharts. In fact, in my experience it was rare that a manufacturer called my division in ODE or the Office of Compliance to request an opinion on a change to a marketed device.

II.F. Postmarket Surveillance, Monitoring Device Experience: Complaints, Medical Devices Reports, Corrective and Preventive Actions

Once a device is placed on the market manufacturers and FDA continue to monitor the device's safety and effectiveness. Three regulatory life cycle activities associated with postmarket surveillance are closely linked and describe the basic requirements of the system for receiving, assessing and taking appropriate action based on postmarket signals. These activities include complaint handling, medical device reports, and corrective and preventive actions. Industry standards and best practices play an important role in formulating the documentation, policies and procedures for these quality management activities.

III. Brief History of MERSILENE MESH for Hernia Repair and Clinical Use of Mesh

Soler, et al., reported on the long history of use of prosthetic materials for the treatment of hernias.[47] He reported that MERSILENE MESH was created in the 1950's and used in the United States since 1954. Chevrel, et al., also refers to the long history of the use of MERSILENE MESH as follows:[48]

[46] Ibid.
[47] Soler M., et al., Polyester (Dacron) Mesh, Abdominal Wall Hernias, Principles and Management, Jan 2001.
[48] Chevrel, J.P., Polyester Mesh for Incisional Hernia Repair, Incisional Hernia, page 327-333. Springer, Berlin, Heidelberg.

The development of prostheses of a polymer of polyester composed of ethylene glycol and terephthalic acid dates back to 1939. It was in 1946 that the first publication appeared in the United States proposing the use of these prostheses in the treatment of major hernias [10]. Polyester prostheses are also known by the name of dacron prostheses and marketed by Ethicon under the name Mersilene. In 1956, Wolstenholme [16] reported in the *Archives of Surgery* the use of these prostheses in 15 cases of inguinal hernia and four cases with loss of abdominal wall substance.

In 1962, Adler [1], again in the *Archives of Surgery*, reported the use of the dacron prosthesis in reinforcing the suture of 31 ventral incisional hernias; in one case, the prosthesis had been used to fill out a loss of substance which had led to a recurrence. In the following years, the dacron prosthesis was increasingly used in hernia repair, as shown by a report on 3000 cases by Bellini in 1969, for example. Shortly afterwards, this prosthesis appeared in France, and articles were written by Jean Rives and his assistants in 1971 relating to 17 cases of major incisional hernias and again in 1973, and there have subsequently been many other reports. Since this date, numerous reports have been made, both by American authors [4, 5, 8, 10] and by French authors [2, 6, 11, 55], to list only the major ones.

FDA has also commented on the surgical mesh for the treatment of hernias. FDA states the following:[49]

> A hernia occurs when an organ, intestine or fatty tissue squeezes through a hole or a weak spot in the surrounding muscle or connective tissue. Hernias often occur at the abdominal wall. Sometimes a hernia can be visible as an external bulge particularly when straining or bearing down.
>
> ***
>
> Hernia repairs are common—more than one million hernia repairs are performed each year in the U.S. Approximately 800,000 are to repair inguinal hernias and the rest are for other types of hernias.1
>
> Non-Surgical
>
> Watchful Waiting - Your surgeon will watch the hernia and make sure that it is not getting larger or causing problems. Although surgery is the only treatment that can repair hernias, many surgical procedures are elective for adult inguinal hernias. Watchful waiting is an option for people who do not have complications or symptoms with their hernias, and if recommended by their surgeon.
>
> Surgical
>
> Laparoscopic - The surgeon makes several small incisions in the abdomen that allow surgical tools into the openings to repair the hernia. Laparoscopic surgery can be performed with or without surgical mesh.

[49] Hernia Surgical Mesh Implants, https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/HerniaSurgicalMesh/default.htm.

Open Repair - The surgeon makes an incision near the hernia and the weak muscle area is repaired. Open repair can be done with or without surgical mesh. Open repair that uses sutures without mesh is referred to as primary closure. Primary closure is used to repair inguinal hernias in infants, small hernias, strangulated or infected hernias.

Hernias have a high rate of recurrence, and surgeons often use surgical mesh to strengthen the hernia repair and reduce the rate of recurrence. Since the 1980s, there has been an increase in mesh-based hernia repairs—by 2000, non-mesh repairs represented less than 10% of groin hernia repair techniques.

The use of surgical mesh may also improve patient outcomes through decreased operative time and minimized recovery time. However, recovery time depends on the type of hernia, the surgical approach, and the patient's condition both before and after surgery.

Information found in medical literature has consistently demonstrated a reduced hernia recurrence rate when surgical mesh is used to repair the hernia compared to hernia repair without surgical mesh. For example, inguinal hernia recurrence is higher with open repair using sutures (primary closure) than with mesh repair2.

Despite reduced rates of recurrence, there are situations where the use of surgical mesh for hernia repair may not be recommended. Patients should talk to their surgeons about their specific circumstances and their best options and alternatives for hernia repair.

Surgical Mesh

Surgical mesh is a medical device that is used to provide additional support to weakened or damaged tissue. The majority of surgical mesh devices currently available for use are constructed from synthetic materials or animal tissue.

Surgical mesh made of synthetic materials can be found in knitted mesh or non-knitted sheet forms. The synthetic materials used can be absorbable, non-absorbable or a combination of absorbable and non-absorbable materials.

Animal-derived mesh are made of animal tissue, such as intestine or skin, that has been processed and disinfected to be suitable for use as an implanted device. These animal-derived mesh are absorbable. The majority of tissue used to produce these mesh implants are from a pig (porcine) or cow (bovine) source.

Non-absorbable mesh will remain in the body indefinitely and is considered a permanent implant. It is used to provide permanent reinforcement to the repaired hernia. Absorbable mesh will degrade and lose strength over time. It is not intended to provide long-term reinforcement to the repair site. As the material degrades, new tissue growth is intended to provide strength to the repair.

Specific surgical mesh products have also been indicated for use for

urogynecological conditions. The FDA Executive Summary at the September 2011 meeting of the Obstetrics and Gynecological Panel of the Medical Devices Advisory Committee provides a brief overview of the development of surgical mesh for the treatment of Stress Urinary Incontinence (SUI) and Pelvic Organ Proplase (POP) (emphasis added).[50]

> "**Surgical mesh was a pre-amendments device** and was classified into Class II (21 CFR §878.3300). Since the 1950s, surgical mesh has been used to repair abdominal hernias. In the 1970s, gynecologists began using surgical mesh products indicated for hernia repair for abdominal repair of POP, and in the 1990s, gynecologists began using surgical mesh for surgical treatment of SUI and vaginal repair of POP. To do so, surgeons would cut the mesh to the desired shape for SUI repair or POP repair and then place the mesh through a corresponding incision. Over time, manufacturers responded to this clinical practice by developing mesh products specifically designed for SUI and POP repair.
>
> In 1996, the Surgical Fabrics (ProteGen Sling) device manufactured by Boston Scientific Corporation became the first pre-configured surgical mesh product cleared via the 510(k) pathway for surgical treatment of SUI. (The ProteGen Sling was cleared with an indication for "pubourethral support," a phrase which implies an indication for treatment of SUI.) However, use of mesh in SUI repair, referred to as slings or tape, did not become common until after the introduction of the Tension-Free Vaginal Tape (TVT™) System, manufactured by Ethicon/GYNECARE, in 1998. This system was based on the work by Ulmsten and colleagues with the Ethicon Prolene hernia mesh. In 2002, GYNEMESH® PS, also manufactured by Ethicon/GYNECARE, became the first pre-configured surgical mesh product cleared for POP repair.
>
> Over the next few years, surgical mesh products evolved into "kits" that included tools to aid in the delivery/insertion of the mesh. The first kit for SUI repair, the Island Biosurgical Bladder Neck Suspension Kit manufactured by Island Biosurgical, Inc., was cleared in 1997. The first kits for POP repair, the AMS Apogee™ System and the AMS Perigee™ System, both manufactured by American Medical Systems, Inc., were cleared in 2004. Surgical mesh kits continue to evolve in regards to introducer instrumentation, tissue fixation anchors, surgical technique, and incorporation of absorbable materials into the mesh intended to increase material compliance.
>
> The FDA premarket notification review process did not request original clinical studies to support clearance of surgical mesh indicated for treatment of SUI or POP. Attempts to establish clinical effectiveness were undertaken later by the clinical community with clinical trials, published studies, and systematic reviews/meta-analyses. Some of this published literature was incorporated into later 510(k) submissions to support market clearance.

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[50] FDA Executive Summary, September 8, 2011, OB/Gyn Advisory Committee Meeting, page 5, http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/ucm262488.htm.

> Premarket clearance of surgical mesh indicated for POP and SUI repair was typically based on pre-clinical bench and animal studies as described in the FDA Guidance Document "Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh" issued on March 2, 1999 (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073791.pdf)."
>
> "From 1992-2010, the FDA cleared 168 510(k)s for surgical mesh with urogynecologic indications

FDA notes the following regarding stress urinary incontinence (SUI):[51]

> "Stress urinary incontinence (SUI) is a leakage of urine during moments of physical activity that increases abdominal pressure, such as coughing, sneezing, laughing, or exercise. SUI is the most common type of urinary incontinence in women.
>
> SUI can happen when pelvic tissues and muscles, which support the bladder and urethra, become weak and allow the bladder "neck" (where the bladder and urethra intersect) to descend during bursts of physical activity. This descent can prevent the urethra from working properly to control the flow of urine. SUI can also occur when the sphincter muscle that controls the urethra weakens. The weakened sphincter muscle is not able to stop the flow of urine under normal circumstances and when there is an increase in abdominal pressure. Weakness may occur from pregnancy, childbirth, aging, or prior pelvic surgery. Other risk factors for SUI include chronic coughing or straining, obesity and smoking.
>
> Surgery to decrease or prevent urine leakage can be done through the vagina or abdomen. The urethra or bladder neck is supported with either stitches alone or with tissue surgically removed from other parts of the body such as the abdominal wall or leg (fascial sling), with tissue from another person (donor tissue) or with material such as surgical mesh (mesh sling).
>
> Surgical mesh in the form of a "sling" (sometimes called "tape") is permanently implanted to support the urethra or bladder neck in order to correct SUI. This is commonly referred to as a "sling procedure."

The following is a description by the Transvaginal Mesh Industry Working Group of pelvic organ prolapse (POP) and its repair in a document presented to the FDA Advisory Committee meeting on September 8, 2011.[52]

> "POP is the condition that results when the normal supporting structures of the vagina deteriorate. The resultant support loss can cause any or all of the following structures to prolapse

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[51] Stress Urinary Incontinence, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm284109.htm. Viewed on 1/29/16.

[52] Transvaginal Industry Working Group, September 8, 2011, OB/GYN Advisory Committee Meeting, page 3.

> (drop out of position): urethra, bladder, bowel, and/or cervix/ uterus/ vaginal vault. This prolapse can produce such symptoms as a sensation of bulge, difficulty with bowel or bladder function, pain and/ or dyspareunia (painful intercourse). Traditional treatment options for POP include hysterectomy, colporrhaphy (plication of pubocervical or rectovaginal fascia), sacro-colpopexy (suturing of vaginal apex to the sacral promontory using either mesh or fascial bridge) performed either abdominally or laparoscopically and sacrospinous fixation (securing the vaginal apex to the sacrospinous ligament). Mesh products were introduced as supporting materials in the surgical treatment of POP to address the high levels of recurrence rates associated with traditional repairs using the patient's own tissue."

FDA's Executive Summary presented before the same FDA advisory committee meeting describes additional aspects of POP and use of mesh:[53]

> The Pelvic Organ Prolapse Quantification (POP-Q) system is commonly used to describe the degree of prolapse. The most distal portion of the prolapsing tissue is measured in the anterior vagina, vaginal apex, and posterior vagina relative to the vaginal opening. The degree of prolapse is described in stages from 0 to 4 based on distance from the vaginal opening. Higher stages indicate more severe prolapse and are more likely to be symptomatic.
>
> Symptomatic POP can be managed conservatively with pelvic floor exercises or by using pessaries, or it can be repaired surgically. Surgical repair of prolapse can be performed transabdominally or transvaginally and may address one or more compartments in the vagina, depending on which areas are affected. The placement of surgical mesh is intended to increase the longevity of surgical POP repairs.
>
> Use of mesh has become common practice for abdominal repair of prolapse (e.g.,sacrocolpopexy) [**7**]. In general, sacrocolpopexy is used to support the vaginal apex and is not performed to repair prolapse that is primarily anterior or posterior. Vaginal repair of prolapse may be augmented with mesh or may be performed by tissue plication and suture only (i.e., native tissue or traditional repair).
>
> In general, mesh products for vaginal POP repair are configured to match the anatomical defect they are designed to correct. Mesh can be placed in the anterior vaginal wall to aid in the correction of cystocele (anterior repair), in the posterior vaginal wall to aid in correction of rectocele (posterior repair), or attached to the vaginal wall and pelvic floor ligaments to correct uterine prolapse or vaginal apical prolapse (apical repair).

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[53] FDA Executive Summary, September 8, 2011, OB/Gyn Advisory Committee Meeting, page 12. FDA reclassified surgical mesh intended for the treatment of POP to Class III, https://www.federalregister.gov/documents/2016/01/05/2015-33165/obstetrical-and-gynecological-devices-reclassification-of-surgical-mesh-for-transvaginal-pelvic.

Iglesia, et al., assessed the use of synthetic mesh for gynecological indications, including MERSILENE MESH, reporting in 1997 that such use had increased over the past 30 years.[54] By 2011 Ghetti, et al., referencing MERSILENE MESH, reported, "Synthetic meshes are commonly used in many urogynecologic procedures, including ASC [ambulatory surgical center procedures] and suburethral slings, and have been utilized in anterior and posterior colporrhaphies."

A 2011 survey of AUGS [American Urogynecological Society] members found overall that 90% of respondents used synthetic mesh for prolapse repair, 93% used synthetic mesh when performing midurethral slings, and 52% when performing vaginal reconstructive surgery for recurrent prolapse.[6] AUGS stated synthetic mesh may provide additional strength and support to native tissue repairs and increase the durability of reconstructive procedures.

MERSILENE MESH is no longer commercially available in the USA based on my search of FDA and other web sites. Former Instructions for Use for MERSILENE MESH described the mesh as "polyethylene terephthalate, the same material used to make MERSILENE Polyester Fiber Suture, Nonabsorable surgical suture U.S.P."[55] The Indications for Use of MERSILENE MESH states as follows:

> *The mesh may be used for the repair of hernia and other fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result.*

D. FDA websites concerning Mesh Use to Treat Hernias, SUI and POP

FDA maintains and periodically updates public information for health care providers, patients, and caregivers regarding surgical mesh use for hernias, SUI and POP as follows:

> Hernia Surgical Mesh Implants:
> https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/HerniaSurgicalMesh/default.htm
>
> Stress Urinary Incontinence:
> https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm284109.htm
>
> Pelvic Organ Prolapse:
> https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm262299.htm

VIII. Opinions

In forming my opinions, I employed methodologies consistently used by health care companies and regulatory authorities to address and

[54] Iglesia, C.B., The Use of Mesh in Gynecological Surgery, Int Urogynecol J (1997) 8:105-115.
[55] See opinion 5.

evaluate premarket, quality system, post-approval and labeling data and information. These methods are also consistent with those utilized by me, the sole member of Ulatowski Consulting, LLC, in the conduct of my assignments with both U.S. and international health care clients manufacturing medical devices including preparation of regulatory submissions and post-market efforts, preparation of regulatory and scientific protocols, labeling and other medical device evaluations. My opinions are also predicated upon the Food, Drug, and Cosmetic Act, the Code of Federal Regulations, Federal Registers, guidance and device standards, and industry practices and standards.

My participation in this litigation and the development of the opinions enclosed herein follow an extensive review process. As described earlier, I possess extensive experience in the medical device industry and draw on this experience in conducting my tasks under the auspices of Ulatowski Consulting, LLC, including the reviews provided herein.

As described, I have performed a thorough and integrated review of the publicly available information and regulatory documents, including those produced during discovery, identified in this report and listed in Exhibit B. I analyzed those documents for their relevance. The employed methodology also included a review of the production documents, any depositions/transcripts, and other materials provided to me by Counsel, or requested by me from Counsel. Upon retrieval, receipt, and review I considered documents for possible inclusion in the evaluation for this report. If additional relevant proprietary documentation was required, and I was unable to independently locate this data/information, I made a request of Counsel for any related documents to be reviewed by me. I analyzed these documents for their regulatory relevance and conformity to industry practices and standards in forming my opinions in the same manner I would have assessed them when I was a premarket evaluator or the chief medical device compliance officer at FDA, and also in the same way I would evaluate them in my current capacity as a consultant to companies on medical device regulatory aspects.

As noted, the employed methods also include my reviews of depositions, corresponding exhibits, potentially associated with regulatory affairs, post-market surveillance, device design and manufacturing, among others. Reviews of depositions and exhibits are critical. Because I have been engaged in all the aspects of medical device design, development and commercialization, I can interpret and evaluate industry testimony.

Based upon my analysis of these documents and information, as well as my experience, knowledge, and training, I have formed opinions with regard to MERSILENE MESH. Each of the opinions set forth below is held to a reasonable degree of scientific and regulatory certainty. My prior testimony is listed in Exhibit C. I have no publications in the past 10 years.

I may use visual aids or demonstrative exhibits, such as diagrams, images, slides or charts, to illustrate and or explain my opinions and analyses in this report, as well as excerpts, charts, and other information from the materials I have cited in my report or identified in the materials reviewed.

I reserve the right to supplement this report and my opinions as discovery progresses in this case.

Opinion 1. It is my opinion the clearance by FDA of MERSILENE containing VICRYL MESH and clearance of GYNEMESH PS established that there was reasonable assurance of safety and effectiveness of these devices and the predicate for these two devices, MERSILENE MESH. Also, by virtue of the clearance by FDA of VICRYL MESH and GYNEMESH PS into Class II they, as well as the predicate MERSILENE MESH, did not present an unreasonable risk of illness or injury.

ETHICON submitted a 510(k), K851086, for VICRYL MESH on March 18, 1985 and FDA cleared the submission on May 21, 1985.[56] VICRYL MESH is a composite of polyglactin 910 and MERSILENE. The FDA clearance established that VICRYL MESH is a Class II surgical mesh device per 21 CFR §878.3300. MERSILENE MESH was a predicate for VICRYL MESH. FDA cannot find a new device equivalent to an adulterated or misbranded device per 21 CFR §807.100. As a result of the clearance, FDA did not find MERSILENE MESH to be in violation of the laws it administers at that time.

The act provides that the controls applicable to Class II devices provide reasonable assurance of safety and effectiveness of devices in the class.[57] The clearance of VICRYL MESH containing MERSILENE by FDA meets one of the Class II controls.[58] As a result, based on the FDA clearance, not only is there reasonable assurance of safety and effectiveness for VICRYL MESH but also its predicate, MERSILENE MESH.

FDA cleared Gynemesh PS on January 8, 2002, K013718.[59] Gynemesh PS was classified into Class II by virtue of the FDA clearance. MERSILENE MESH is one of the predicate devices for Gynemesh PS. As above, FDA did not find MERSILENE MESH, the predicate for Gynemesh PS, to be in violation of the laws it administers at that time otherwise the clearance could not proceed. Again, FDA confirmed by the Gynemesh PS clearance that there was reasonable assurance of the safety and effectiveness of Gynemesh PS and MERSILENE MESH.

As I note above in this report, FDA placement of a device in Class II represents a determination that, with whatever special controls the FDA has imposed, it does not present "a potential unreasonable risk of illness or injury." There was not a potential unreasonable risk as determined by FDA's Class II clearance actions for VICRYL MESH and Gynemesh PS and placement of the pre-1976 MERSILENE MESH into Class II.

In sum, based on the clearance of VICRYL MESH and Gynemesh PS based, in

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[56] VICRYL MESH, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K851086.

[57] 21 U.S.C. 360c. Controls include, for example, registration and listing, quality system requirements, postmarket reporting, and 510(k) clearance.

[58] Reasonable assurance of safety and effectiveness by meeting the 510(k) Class II control is not the same as the Class III control, which requires a determination of safety and effectiveness.

[59] 510(k) summary, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K013718. Ethicon modified Gynemnesh PS labeling to exclude transvaginal use.

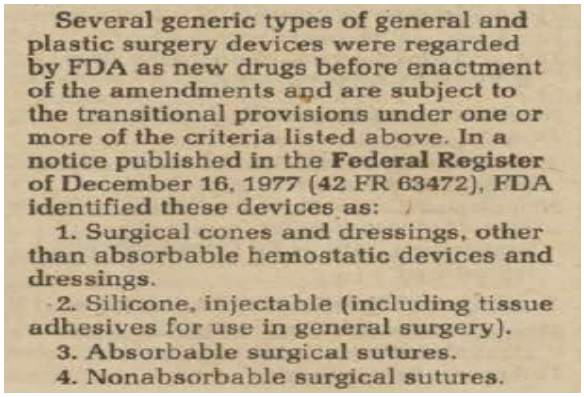
part, on the predicate MERSILENE MESH, it must be concluded that FDA determined that MERSILENE MESH at the time of these clearances, and indeed dating back to the classification process, was reasonably safe and effective by the Class II statutory standard and did not present unreasonable risk of illness or injury.

Opinion 2. It is my opinion that polyethylene terephthalate, the primary material used in MERSILENE MESH, is safe and effective based on FDA's new drug approval decision on MERSILENE sutures.

I believe, based on the regulatory history of MERSILENE containing devices, that FDA considered MERSILINE to be clinically acceptable for its intended use.

Polyethylene terephthalate is the primary component in MERSILENE MESH.[60] MERSILENE MESH consists of the same material as the MERSILENE suture.[61] Polyethylene terephalate was first used as a surgical material for many years as I have explained in the MERISLENE history in this report.

MERSILENE sutures were first regulated by FDA as a drug prior to the enactment of the 1976 medical device amendments to the Federal Food, Drug and Cosmetic Act as follows:[62]



Several generic types of general and plastic surgery devices were regarded by FDA as new drugs before enactment of the amendments and are subject to the transitional provisions under one or more of the criteria listed above. In a notice published in the **Federal Register** of December 16, 1977 (42 FR 63472), FDA identified these devices as:

1. Surgical cones and dressings, other than absorbable hemostatic devices and dressings.
2. Silicone, injectable (including tissue adhesives for use in general surgery).
3. Absorbable surgical sutures.
4. Nonabsorbable surgical sutures.

FDA approved a New Drug Application (NDA), NDA 12815, for MERSILENE sutures prior to 1976.[63] An order approving a new drug is a determination by FDA that the drug is safe and effective.[64]

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[60] The composition of MERSILENE suture or mesh has been described in labeling either as POLY (ethylene terephthalate) or polyethylene terephthalate. Both are the same composition.

[61] ETH-00805.

[62] 47 FR 2810 (January 19, 1982).

[63] List of 15 MERSILENE suture supplements approved by FDA as PMA supplements through 1988, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?start_search=1&applicant=&tradename=&productcode=&pmanumber=N12815&supplementnumber=&advisorycommittee=&docketnumber=&supplementtype=&expeditedreview=&ivdproducts=off&combinationproducts=off&decisiondatefrom=&decisiondateto=&noticedatefrom=&noticedateto=&PAGENUM=500&sortcolumn=pn_desc_sn_desc.

NDAs for sutures regulated as drugs, called transitional devices after the medical device amendments were enacted in 1976, were transferred from the Center for Drug Evaluation and Research to the Center for Devices and Radiological Health after 1976 and then were regulated as devices. ETHICON was then required to comply with PMA reporting requirements for MERSILENE sutures until those PMA requirements were changed to 510(k) requirements by the FDA reclassification process.

On May 31, 1991, FDA reclassified poly (ethyelene terephthalate) sutures from Class III to Class II.[65] The Federal Register notice refers to the consideration of the suture by the General and Plastic Surgery Panel of the FDA and an open meeting of the Panel on October 20, 1988.[66] The classification regulation for this type of suture is codified under 21 CFR §878.5000. By this action FDA found that the suture no longer presented a potential unreasonable risk of illness or injury.

Besides the approved NDA before 1976 and nonabsorbable suture reclassification from Class III to Class II discussed above after 1976, FDA had another major opportunity to assess the safety and effectiveness of MERSILENE MESH when it classified surgical mesh. When FDA proposed the classification of the preamendments surgical mesh in 1982[67] it considered the recommendations of the General and Plastic Surgery, Orthopedic, and Gastroenterology and Urology Device Panels. In classifying surgical mesh the Panels relied upon their clinical experience with mesh, their review of published clinical data, and their assessment of the risks posed by mesh to health as stipulated in the act regarding classification procedures.[68] The classification rule references clinical data with MERSILENE MESH.[69] FDA finalized the classification of surgical mesh, of which MERSILENE MESH is one specific example, into Class II in 1988.[70]

Classification of surgical mesh into Class II established that under the act reasonable assurance of safety and effectiveness of surgical mesh would be based upon general controls, including, for example, 510(k) submissions, and any special controls FDA finalized for mesh.

I find no evidence on FDA's web site of any enforcement action taken by FDA against MERSILENE suture or mesh. There is one 2016 Class II recall of a MERSILENE Tape (ligature/suture) due to incorrect instructions for use placed in the packaging.[71]

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[64] 21 U.S.C. §355.
[65] 56 FR 24685 and 68 FR 32984.
[66] Public records of this meeting are no longer available on FDA web site.
[67] 47 FR 2810 (January 19, 1982).
[68] 21 USC §360c(b)-(d).
[69] 47 FR 2810, page 2817 and references 6-8.
[70] 53 FR 23856 (June 24, 1988).
[71] MERSILENE TAPE (ligature) recall https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=148716. This recall indicates that MERSILENE TAPE (ligature) is an exempt Class I device not subject to 510(k) submission. A surgical ligature is tied around an anatomical structure. See literature for use of this tape, for example, in cerclage.

OPINION 3: Physicians are permitted to use any legally marketed device for any condition or disease regardless whether or not such disease or condition is included in the labeling.

The Federal Food, Drug and Cosmetic Act states the following regarding the practice of medicine:[72]

> Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship. This section shall not limit any existing authority of the Secretary to establish and enforce restrictions on the sale or distribution, or in the labeling, of a device that are part of a determination of substantial equivalence, established as a condition of approval, or promulgated through regulations. Further, this section shall not change any existing prohibition on the promotion of unapproved uses of legally marketed devices.

This provision of the law limits FDA's jurisdiction over a health care practitioner's use of MERSILENE MESH for either the indications for use in the labeling for MERSILENE MESH or for any other use the practitioner believes is appropriate for his/her patient. Use of a device by a health care practitioner for a disease or condition not in the labeling is commonly called "off-label" use.[73] Off-label use of MERSILENE MESH could include, for example, the use of the mesh in treatment of SUI or POP.

OPINION 4: Clinical literature demonstrates many years of clinical use of MERSILENE sutures and mesh.

I searched PUBMED for articles referring to MERSILENE.[74] This resulted in 733 publications using the applied search terms. The publications are both domestic and foreign. The publications include use of both mesh and sutures for various clinical applications or in some there is only a reference to MERSILENE. A PUBMED search of MERSILNE MESH results in 277 publications.[75] A search of MERSILENE MESH for hernia results in 95 publications from 1963 to 2014.

Generally, the papers on MERSILENE MESH for the treatment of hernias describe clinical evidence consisting of clinical studies with up to hundreds of subjects and case reports on various types of hernias. In sum, the papers predominantly report on the safe and effective clinical use of MERSILENE MESH in treating hernias and in preventing recurrence of hernias. While there are reported adverse effects these effects are of types reported for mesh use in hernia surgery, e.g., pain, infection and adhesion as documented by FDA in its information on hernia mesh implants.[76]

There are 26 papers in my search of MERSILENE MESH and SUI using the

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[72] 21 U.S.C. §396.
[73] https://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm.
[74] Search on 9/21/18 using search terms MERSILENE, MERSILENE MESH, MERSILENE MESH SUI or POP.
[75] Literature (Heneghan CJ, et al. 2017) incorrectly refers to MERSILENE MESH clearance in 1985. This was in fact VICRYL MESH described in this report.
[76] Hernia Surgical Mesh Implants, https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/HerniaSurgicalMesh/default.htm.

applied search terms. Again, these papers are both domestic and foreign. The papers date from 1973 back to 2009. Likewise, there are 33 papers in a search of MERSILENE MESH and POP dating from 1970 to 2018.[77] It is not clear from all the papers that the devices used are Ethicon MERSILENE MESH. The clinical use of MERSILENE MESH for POP and SUI are off-label in the USA as my report describes above.

I was provided 29 papers or book chapters dating from 1961 to 2009 concerning MERSILENE suture, MESH, "ribbon" or "gauze" for the treatment of various conditions including, for example, hernias or urogynecological conditions. Most of the papers concern SUI. I reference at least one of these papers in my background section in this report. I was also provided a document concerning sterilization of MERSILENE MESH.

One paper references MERSILENE but used Gore-Tex material [Horbach, et al.]. The papers are both domestic and foreign. It is not clear from several papers whether the device used is an Ethicon MERSILENE product. One paper describes trimming of the "ribbon" [Wohlrab, et al.]. In general the papers describe the clinical use of MERSILENE products including benefits and risks.

In sum, the papers show a long history of use of MERSILENE containing devices. The papers consist mainly of clinical evidence documenting clinical use of MERSILENE devices for various indications, their benefits and risks, and the evolution of use of MERSILENE devices.

OPINION 5: The labeling for MERSILENE MESH met the FDA device labeling regulatory requirements and was not required to include precautions, warnings and adverse effects for indications not in the labeling.

The term "labeling" means all labels and other written, printed or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.[78] The term "label", in part, means a display of written, printed, or graphic matter upon the immediate container of any article.[79] Labeling includes important information to the end user to enable him or her to use the product safely and effectively for the indications listed therein.

Labeling requirements for medical devices are provided in 21 CFR Part 801, Labeling. The labeling regulation describes the form and content of labeling, provisions for devices labeled for over the counter use, and specific statements for certain devices. Adequate directions for use, 21 CFR §801.5, provide labeling requirements for devices intended for lay use, i.e., over-the-counter product.

Content and Format of Prescription Labeling

An exemption from adequate directions for lay use is provided for prescription devices. As noted in the regulation:

> *A device which, because of any potentiality for harmful effect,*

[77] There are a few papers on use of MERSILENE Tape for SUI and POP.
[78] Section 201(m) of the act (21 USC §321(m)).
[79] Section 201(k) of the act (21 USC §321(k)).

or the method of its use, or the collateral measures necessary to its use is not safe except under the supervision of a practitioner licensed by law to direct the use of such device, and hence for which "adequate directions for use" cannot be prepared, shall be exempt from section 502(f)(1) of the act if all the following conditions are met:

(a) The device is:

(1)(i) In the possession of a person, or his agents or employees, regularly and lawfully engaged in the manufacture, transportation, storage, or wholesale or retail distribution of such device; or

(ii) In the possession of a practitioner, such as physicians, dentists, and veterinarians, licensed by law to use or order the use of such device; and

(2) Is to be sold only to or on the prescription or other order of such practitioner for use in the course of his professional practice.

(b) The label of the device, other than surgical instruments, bears:

(1) The statement "Caution: Federal law restricts this device to sale by or on the order of a ____", the blank to be filled with the word "physician", "dentist", "veterinarian", or with the descriptive designation of any other practitioner licensed by the law of the State in which he practices to use or order the use of the device; and

(2) The method of its application or use.

(c) Labeling on or within the package from which the device is to be dispensed bears information for use, including indications, effects, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the device can use the device safely and for the purpose for which it is intended, including all purposes for which it is advertised or represented: Provided, however, that such information may be omitted from the dispensing package if, but only if, the article is a device for which directions, hazards, warnings, and other information are commonly known to practitioners licensed by law to use the device. Upon written request, stating reasonable grounds therefore, the Commissioner will offer an opinion on a proposal to omit such information from the dispensing package under this proviso.

(d) Any labeling, as defined in section 201(m) of the act, whether or not it is on or within a package from which the device is to be dispensed, distributed by or on behalf of the manufacturer, packer, or distributor of the device, that furnishes or purports to furnish information for use of the device contains adequate information for such use, including indications, effects, routes, methods, and frequency and duration of administration and any relevant hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to employ the device can use the device safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented. This information will not

be required on so-called reminder--piece labeling which calls attention to the name of the device but does not include indications or other use information.

(e) All labeling, except labels and cartons, bearing information for use of the device also bears the date of the issuance or the date of the latest revision of such labeling.

Mersilene Mesh Labeling

The Instructions for Use (IFU) for MERSILENE MESH contained in the 2001 510(K) for Gynemesh PS met the regulatory requirements listed above which came into effect after MERSILENE MESH was first marketed. The IFU contains clear and concise Indications for Use, Description of the device, its Actions, and Contraindications, Warnings, Precautions, Adverse Reactions, surgical recommendations and how the product is supplied.[80] The Adverse Reactions section includes fistula and extrusion as potential reactions.

I was provided subsequent 2004 and 2005 multiple language editions of MERSILENE MESH labeling indicating CE marking for the device.[81] The indications for use in the 2004 and 2005 IFU are identical to the version in the 2011 Gynemesh PS submission, i.e., hernia and other fascial deficiencies. The contraindications in the IFU in 2001 were moved in the 2004/2005 IFUs to the Warnings/Precautions/Interactions IFU section. The adverse reactions in the 2001 supplied IFU are now in the Warnings/Precautions/Interactions IFU section of the 2004/2005 versions and a revised Adverse Reaction IFU section in 2004/2005 refers to transitory inflammatory reaction at the wound site and a transitory foreign body response as well as it may potentiate an infection. FDA also reports these adverse reactions in its information on surgical mesh in 2018.[82]

There remains no mention in any of the IFUs of any aspect of off-label use. There is no regulatory requirement or industry standard or practice to include information on off-label use of a device in an IFU. Inclusion of off-label information in an IFU could be construed by FDA as illegal promotion for that off-label use, therefore making the IFU misbranded.[83]

The IFUs are consistent with industry standards and practices for device labeling, including surgical mesh in the time period represented in the IFUs. I have no knowledge based on my research when MERSILENE MESH was no longer on the market in the USA.

In sum, the IFUs I reviewed for MERSILENE MESH were compliant with FDA labeling regulations, the form and content of the IFUs met industry standards and practices for device labeling.

I reserve the right to amend my opinions pending further discovery and

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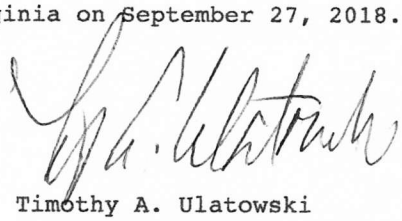
[80] ETH-00805.
[81] ETH.MESH.21656729-32. CE mark indicates the device may be placed on the market in Europe.
[82] Hernia Surgical Mesh Implants, https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/HerniaSurgicalMesh/ucm317438.htm.
[83] 21 U.S.C. §331.

to respond to any expert reports for Plaintiffs regarding this device.

Executed in Herndon, Virginia on September 27, 2018.



Timothy A. Ulatowski

APPENDIX A: CV

Timothy A. Ulatowski

1103 Arboroak Place · Herndon, Virginia 20170

703-404-2997 timothy.ulatowski@verizon.net

Consultant, Medical Devices

Extensive Regulatory Experience ~ Risk Management ~ Technical Expert

A unique medical device consultant with extensive experience in both premarket evaluation of new medical devices and enforcement of FDA laws and regulations. Over 36 years of significant public health achievements, creating major regulatory programs and policies, developing and implementing strategic and risk management plans, and building collaborations with global regulatory partners and industry. Proven skills in advising industry on regulatory issues, assessing compliance and enforcement actions, evaluating premarket documents, managing and supervising large organizations, resolving complex technical and scientific problems of individual firms to those of national and international scope, and communicating to diverse audiences.

Selection of Notable Accomplishments

Hands on technical leadership of numerous compliance, enforcement and recall actions, many of national and global importance

Initiated use of novel corporate enforcement actions

Created effective internal quality management system used as a model program in FDA

Lead author of international guidance documents on aspects of the Global Harmonization Task Force medical device regulatory model

Recognized in “Top 100” of medical device professionals/MDDI

Primary reviewer of hundreds of Premarket Notifications, Investigational Device Exemptions, Premarket Approval Applications, recalls and compliance actions

Leader of team that developed the current FDA device standards program

Author of many key FDA premarket guidance documents, technical standards and publications

FDA key witness in federal court (US v Abtox), contributor to many court cases, advisor to DOJ and FDA criminal investigations office

Lead for agency on many GAO, OMB and Congressional activities

FDA spokesperson to major press and to large audiences

HHS Team Leader and technical expert remediating Anthrax contamination of Senate and Postal Service buildings

Creator of FDA/CDC/EPA tripartite collaborations on chemical germicides and co-author of current FDA/EPA national regulatory scheme for chemical germicides

Co-author and collaborator on sharps injury prevention guidance, related OSHA and NIOSH regulations and policies, resulting in documented reduction of injuries

Recipient of numerous major FDA awards

Professional Experience

Independent Consultant

May 2014 - present

Becker & Associates Consulting Inc./NSF Health Sciences: Expert Consultant then employee

September 2011 – April 2014

- Provided effective and timely solutions to a variety of medical device regulatory issues
- Created and evaluated premarket submissions, quality systems, compliance, and device reporting
- Provided Training on FDA medical device requirements
- Expert witness

NDA Partners LLC: Principal

January 2011 – June 2012

- Advised clients on FDA regulations and law regarding product submissions, compliance and enforcement actions, and postmarket surveillance activities
- Served as an expert witness in litigation
- Conducted due diligence

FDA, CDRH: Director, Office of Compliance and Senior Advisor for Enforcement

January 2003 – January 2011

- Managed and supervised office of four divisions and 180 professional staff responsible for ensuring compliance with medical device laws and regulations
- Directed FDA device quality system and bioresearch enforcement programs
- Directed inspection assignments and assessed quality system and bioresearch monitoring inspection reports and company/investigator/sponsor/IRB responses to determine violations
- Worked with all FDA districts, ORA and drug, biologics and food compliance executives to formulate enforcement strategies and actions
- Hands on evaluation and management of recalls, device advertising and promotion, MDRs, registration and listing, and medical device field resource allocation and prioritization
- Created new device enforcement policies and programs, directed implementation of the Commissioner's strategic action items, and participated in executive strategic planning at the agency and center levels
- Co-leader of FDA Medical Device Field Committee, an ORA/CDRH collaboration

- Initiated comprehensive training program for compliance staff and web-based information for the public
- Co-leader of 2010 user fee legislation post market committee, devising proposals and strategies with key Center and Agency staff for next round of legislation
- Senior Device Enforcement Advisor September 2010 – January 2011

FDA, CDRH: Head of USA Delegation, Global Harmonization Task Force and FDA representative to GHTF Study Group 1 Premarket

January 1995 - October 2010

- Managed the activities of the USA FDA participants to the GHTF Steering Committee and the five study groups; collaborated with USA industry task force members, USA leader on the GHTF Steering Committee for last four years
- Coordinated creation and review of documents and recommended agency decisions on pending documents to Center Director
- Primary author of several GHTF documents, including the original premarket "STED" document, and Global Model document, which are now used internationally
- Frequently trained international government staff on GHTF and FDA procedures

FDA, CDRH/Office of Device Evaluation: Director, Division of Dental, Anesthesiology, General Hospital, and Infection Control Devices

December 1996 – January 2003

- Managed premarket activities, such as review of premarket submissions and investigational applications, panel meetings, guidance development, and collaborative support for other CDRH offices
- Led development of the division during a major reorganization
- FDA lead on numerous international standards committees, reengineering task groups, and interagency task forces dealing with significant public health issues
- Succeeded in reducing review times while improving the quality and rigor of reviews
- Primary reviewer on numerous 510(k)s, IDEs, and PMAs
- Agency and ISO technical expert on medical device sterilization and disinfection

Prior to 1996 FDA and other experience, short summary

Device Evaluation Associate Director, Branch Chief and front line 510(k), IDE, and PMA reviewer

Director, Investigational Device Staff, IDE application review and protocol advice

New Drug Evaluation Product Manager, NDA and IND activities and advisory committee exec sec

Microbiologist, National Center for Antibiotic Analysis, drug assessments

Prior to college and FDA career: US Army 1968 – 1971

Education

- Master of Science/Physiology with Biomedical Engineering emphasis, 1988 GPA 4.0

Georgetown University School of Medicine

- Bachelor of Science/Microbiology, 1974 cum laude

Pennsylvania State University

APPENDIX B: Materials Reviewed and Public Sources of References

Federal Register
Code of Federal Regulations
Government web sites
Federal Food, Drug and Cosmetic Act

Additional reference list to be supplied by Butler Snow

Appendix C: Prior Testimony

Depositions:

University of Pittsburgh of the Commonwealth System of Higher Education d/b/a University of Pittsburgh v. Varian Medical Systems, Inc.

Civil Action No.: 2:08-cv-01307 (USDC, Western District of Pennsylvania)

David M. Kloss, et al, v. I-Flow Corporation, et al, Case No. 2:10-cv-00295-JFC (USDC, Western District of Pennsylvania)

Retractable Technologies, Inc. and Thomas Shaw v. Becton, Dickinson and Company, Civil Action No.2:08-cv-16 (Folsom) (USDC, Eastern District of Texas Marshall Division)

Diagnostic Devices Inc, v. Pharma Supply, Inc. et al, Diagnostic Devices Inc, v. Taidoc Technology Corporation, Case No.3:08-CV-00149-MOC-DCK (USDC, Western District of North Carolina, Charlotte Division)

Brenda F. Kitrosser v. Nuvasive, Inc. et al., Case No: 37-2009-00099700-CU-MM-CTL [Consolidated with Case No: 37-2010-00099400-CU-PO-CTL] (Superior Court of the State of California In and For the County of San Diego, Central Branch)

Superior Court of New Jersey, Law Division, Atlantic County

In re Pelvic Mesh/ Gynecare Litigation, Case No.291 CT, Master Case 6341-10

Jackson, et al v DePuy Orthopedics, No. CAL 10-32147 (Prince George's County, MD)

Strum v. DePuy Orthopaedics, Inc., et al., No. 11 L 009352 (Circuit Court, Cook County, Illinois)

Dorney-Madgitz v. DePuy Orthopedics, Inc., et al., 5:11-cv-001240-RBS (USDC, Eastern District of Pennsylvania)

Weinstat, et al. v. Dentsply International, et al., San Francisco Superior Court No. CGC-04-432370

Braun v. Medtronic Sofamor Danek, USDC, District of Utah, Central Division, Case 2:10-cv-01283

Connie Schubert and Kevin Schubert v. Ethicon, Inc., Ethicon Women's Health and Urology, a division of Ethicon, Inc., Gynecare, and Johnson and Johnson, et. al., In the Circuit Court of Jasper County, Missouri at Joplin, Case No. 10AO-CC00219

Sekisui America Corporation and Sekisui Medical Co., Ltd. v. Richard Hart and Mary Louise Trudel-Hart, USDC, Southern District of New York, Case 1:12-cv-03479-SAS (for Plaintiff)

Carol Lewis and Kenneth Lewis v. Ethicon, USDC, Southern District of West Virginia, MDL No. 2327

April Christine Cabana v. Medtronic Inc. (et al), Superior Court of the State of California, County of Los Angeles, Case No. BC 465 313

Christine Napolitano v. Synthes, Inc., USDC, District of Connecticut, Civil Action 3:09-CV-00828

Herlihy-Paoli v. DePuy Orthopedics, Inc., et al, 3:12-CV-04975-K (USDC, Northern District of Texas, Dallas Division)

City of Lakeland Employees Pension Plan v. Baxter International Inc., No. 10-cv-6016, USDC, Northern District of Illinois

Smith v. Baxano, Inc. et al, Superior Court of Washington for Snohomish County, Case No. 13-2-02714-1

Andrea Smith v DePuy Orthopedics, et al., District Court of Tulsa County, Oklahoma, No. CJ-2011-05804

Zimmer NexGen Knee Implant Products Liability Litigation, USDC, Northern District of Illinois, Eastern Division, MDL No. 2272, Master Docket No.:1:11-cv-05468

Sandra Garcia v Rodolfo J. Walss, MD, Johnson & Johnson, Inc. and Ethicon, Inc., District Court, 103rd Judicial District, Cameron County, Texas, Cause No. 2013-DCL-3511-D

Laura Ness v Depuy Orthopedics, Inc., et al., In the Circuit Court for Baltimore City, Case No. : 24-C-14-002465

Consolidated Fresenius Cases, Commonwealth of Massachusetts, Middlesex SS., Superior Court Department of the Trial Court, Civil Action No. 2013-03400-O Session

Aoki, Christopher, Greer, Klusmann, Peterson, Thibodeau (separate Plaintiffs) v DePuy Orthopedics, Inc. et al,. USDC, Northern District of Texas, Dallas Division, MDL No. 2244

Center City Periodontists, P.C., et al. v. Dentsply International, Inc., Eastern District of Pennsylvania, Civil Action No. 10-00744.

Michael Parker, Individually and Amy Parker, Individually v. Veronica A. Vasicke, MD; Bluegrass Orthopedics & Hand Care, PSC; and I-Flow Corporation, Fayette Circuit Court, Eighth Division, Civil Action No. 12-CI-3543.

Mary N. Insall, as the Executrix of the estate of John N. Insall, Petitioner and Zimmer, Inc. Respondent, American Arbitration Association, Chicago, Illinois, Case No. 01-15-0002-0601.

Dennis Brian Anders, et al. v Medtronic, Inc and Medtronic Sofamor Danek USA Inc, State of Missouri, 22nd Judicial Circuit Court, City of St. Louis, Case File No. 1322-CC10219.

Rachel Dennert v Medtronic, Inc. et al, USDC, District of Connecticut, Civil No: 3:11-cv-01229-SRU.

Dana Lemay, et al., v. Johnson and Johnson , et al., Superior Court Judicial District of Waterbury Complex litigation Docket, Docket No. X06-UWY-CV-13-6022061-S.

Scott Shields and Phyllis Shields v. Medtronic, Inc., Matthew McCormick, Southwestern Illinois Health Facilities, Inc. a/k/a Anderson Hospital and Dr. EI S. Lin, Circuit Court, Third Judicial Circuit, Madison County, Illinois, Case No. 2014-L-1222.

Plaintiffs v 3M Company and Arizant Healthcare, Inc., USDC, District of Minnesota, MDL No. 15-2666 (JNE/FLN).

Gary Gladen and Nancy Gladen v Johnson and Johnson Services, Inc.; Johnson and Johnson; DEPUY Orthopedicas, Inc., Superior Court of the State of California, County of San Francisco, Case No. CGC-11-514508.

Gary Bryan Brackin, surviving spouse of Pamela W. Brackin v Medtronic, Inc. et al., USDC Western District of Tennessee Western Division, Case No. 2:17-cv-2101.

Court Testimony:

Strum v. DePuy Orthopaedics, Inc., et al., No. 11 L 009352 (Circuit Court, Cook County, Illinois).

Brenda F. Kitrosser v. Nuvasive, Inc. et al., Case No: 37-2009-00099700-CU-MM-CTL [Consolidated with Case No: 37-2010-00099400-CU-PO-CTL] (Superior Court of the State of California In and For the County of San Diego, Central Branch).

Weinstat, et al. v. Dentsply International, et al., San Francisco Superior Court No. CGC-04-432370.

Sekisui America Corporation and Sekisui Medical Co., Ltd. v. Richard Hart and Mary Louise Trudel-Hart, USDC, Southern District of New York, Case 1:12-cv-03479-SAS.

Becky S. Anderson v. Medtronic, Inc. (et al), Superior Court for the State of Washington, County of King, No. 12-2-17928-0 SEA.

Donald Gustafson v. Zimmer, Inc., District Court, Collin County, Texas, 366th Judicial District, Cause No. 366-03111-2011.

Herlihy-Paoli v. DePuy Orthopedics, Inc., et al, 3:12-CV-04975-K (USDC, Northern District of Texas, Dallas Division).

Andrea Smith v DePuy Orthopedics, et al., District Court of Tulsa County, Oklahoma, No. CJ-2011-05804.

Alysia Ogburn-Sisneros, as personal representative of the estate of Billy Ogburn, Sr., Plaintiff v. Fresenius Medical Care Holdings, Inc.d/b/a Fresenius Medical Care North America, Inc, Fresenius USA, Inc., Fresenius USA Manufacturing, Inc., Fresnius USA Marketing, Inc., and Fresenius USA Sales, Inc., Defendants, Commonwealth of Massachusetts, Superior Court Department, Civil Action No. 13-5050.

Center City Periodontists, P.C., et al. v. Dentsply International, Inc., Eastern District of Pennsylvania, Civil Action No. 10-00744.

Aoki, Christopher, Greer, Klusmann, Peterson, Thibodeau (separate Plaintiffs) v DePuy Orthopedics, Inc. et al,. USDC, Northern District of Texas, Dallas Division, MDL No. 2244.

Andrews, Davis, Metzler, Rodriguez, Standerfer, Weiser v. Depuy Orthopedics, USDC, Northern District of Texas, Dallas Division, MDL 3:11-MD-2244-K.

Mary N. Insall, as the Executrix of the estate of John N. Insall, Petitioner and Zimmer, Inc. Respondent, American Arbitration Association, Chicago, Illinois, Case No. 01-15-0002-0601.